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AI-based Design Workflow of De-Novo Antigens by Epitope Scaffolding

De-novo protein design allows a wider exploration of protein folding space than directed evolution and has been profitable employed in several fields of biochemistry and medicine, as metalloproteins design 1 and in-vitro diagnostics (IVD) 1. Among other design tasks, de novo protein binders can now be obtained with high success-rate that are highly specific towards a series of biological targets, thanks to the recent advances in the AI field [3,4,5]. Despite that, IVD industry still heavily relies on antibodies, as they are cheaper, and their production is well standardized. Therefore, a de-novo antigen may virtually speed-up and support the production of better antibodies. In this work, we present a workflow to scaffold small proteins (˜50AA) around a known antigen epitope to elicit higher immune response in host organisms. The workflow is divided in two cyclic phases: generation and validation, each one using task-specific AI-models. The generation phase starts by creating several backbones of small scaffolds via diffusion models 1 around a chosen epitope, whose position and residues are held constant during the process. Subsequently, protein language models 1 are used on such backbones to assign the sequences. The structure of the generated sequences is then predicted through in-silico folding models 1 and the most promising sequences are screened in-silico for immunogenicity with MaSIF 1, a model evaluating protein-protein interaction sites based on geometric neural network. The methodology has been performed on one epitope of HPV-16, obtaining 6 different small proteins which are currently being screened in-vitro. The proposed workflow is fully generalizable to any epitope, and we envision that it can pose a novel methodology in the design of the de-novo antigens.

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